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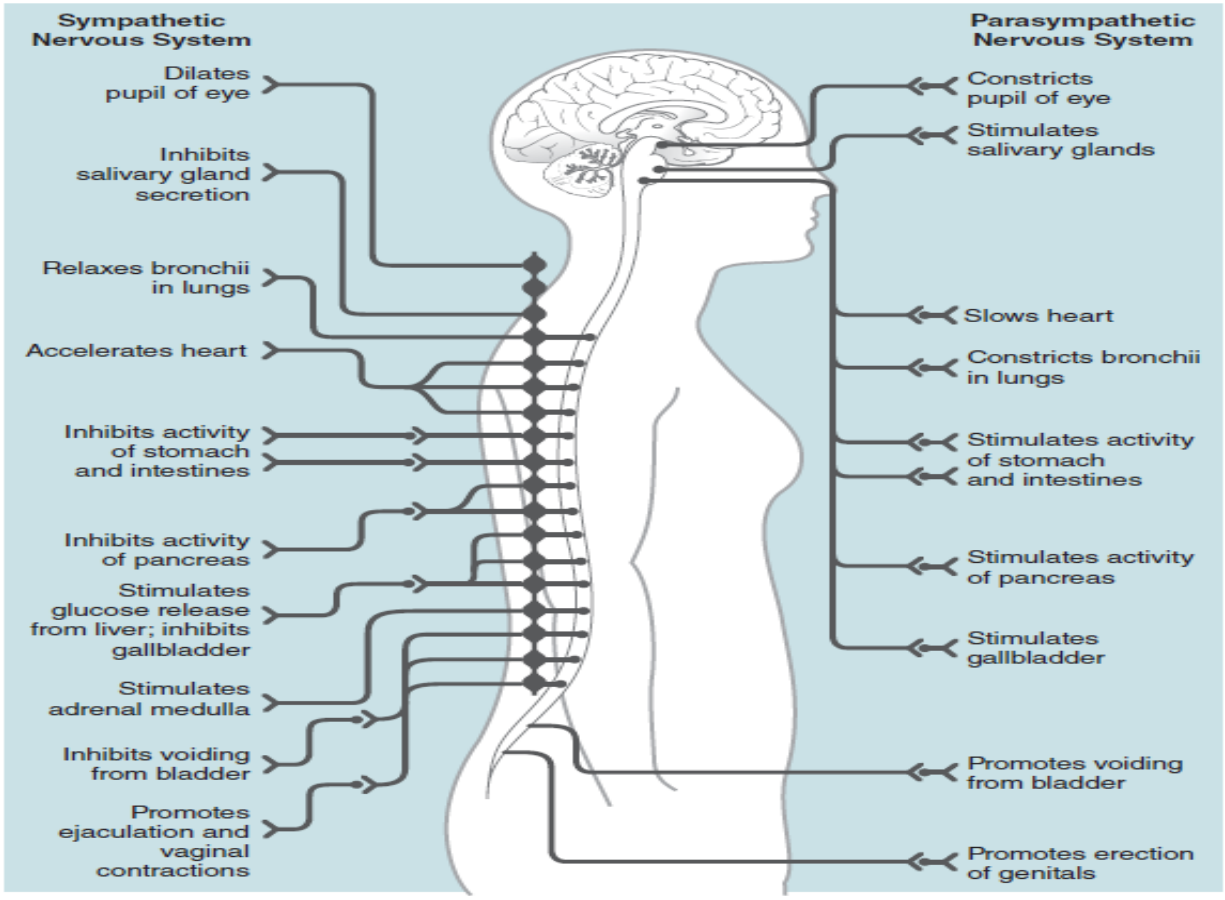
General Notions about ANS II

Points of Lecture

- **Site of Action of Acetyl choline (Where it will Act)**
- **Cholinergic Transmission**
- **Drugs Acting on It**



We have started studying about receptors and you know the classification of receptors and the main target sites. The second lecture was about Adrenergic system, in the last lecture we studied about Adrenaline, Nor-Adrenaline and Dopamine how is the action of each of them and their effects on effector organs. In this Lecture we are going to complete the second part of the cholinergic system.

Cholinergic transmission if you remember we have studied the adrenergic transmission we said there are 5 steps in adrenergic transmission and then we will study your main points the act on these transmission from the decrease or increase of acetylcholine and with which clinical disease we use them because we have known in the adrenergic system is mainly concern with the Cardiovascular system (e.g. Hypertention, MI, Bronchoconstriction and so on) we will see about acetyl choline we will start the first point:

- ✓ **Site of Action of Acetyl choline (Where it will Act)**

You know that there are 2 divisions of the Autonomic Nervous system. The adrenergic system comes from the thoracic and sacral part but the cholinergic is usually arise from the cranial part we have the 10^{th} and 11^{th} cranial nerves will come from the cholinergic system. The first neuron that comes from the cranial part it is called the First neuron that it releases acetylcholine, the second neuron innervate the effector organ (e.g. the Eye, Heart, smooth muscles, GI tract, Bladder and so on) all the internal organs they are a target for acetyl choline or adrenaline.

The connection between the first neuron and the second neuron called the Ganglia if they are in parasympathetic cholinergic system or adrenergic system we call it Autonomic ganglia.

The main transmitter in the ganglia is acetylcholine. It is the main transmitter in the adrenergic and cholinergic ganglia that means when there is activation for acetyl choline → increase Acetylcholine release from the first neuron act with its receptors in the second neuron that is *Nicotinic Ganglionic receptors* that means in ganglia acetylcholine works and the receptors present are *Nicotinic ganglionic receptors.* Why we call it *Nicotinic ganglionic receptors?*

We have 2 types of receptors *Muscarinic and Nicotinic receptors*. The Nicotinic receptors differ into:

1. *Nicotinic Ganglionic (NG)*
2. *Nicotinic Muscular (NM)*

We called the nicotinic because nicotine is the drug that works on them only and we call Muscarinic because from Muscarine (a plant Alkaloid) that interact only with muscarinic receptors that means nicotine cannot interact with muscarinic and vice versa. So if we have a drug from outside body that have nicotinic structure will interact with nicotinic receptors and if we have a drug that have muscarinic structure it will interact muscarinic receptors. The endogenous acetylcholine act with both muscarinic and nicotinic receptors because of the flexibility it changes its structure according to the need if the need in a situation to act on nicotinic receptors it will change its structure to nicotinic and so for Muscarinic receptors, but we cannot from outside give a drug that can change its structure. Outside given drugs may be nicotinic or muscarinic drug (N.B Endogenous Acetylcholine can change its structure).

Nicotinic Ganglionic (NG): it means that nicotinic act on ganglia. If there is activation for the autonomic ganglia → increase acetylcholine release→ interact with ganglionic receptors→increased parasympathetic and sympathetic action so it cause disturbance how is that BP increase ,decrease , increase contractility of heart so there is no drug that act like acetyl choline. But there are drugs that have nicotinic action and there are drugs that have muscarinic action. If we get a drug that block the ganglia we call it a *Ganglionic blocker (e.*g. *Trimethaphane*) it's a ganglionic blocker, the effect of this drug is it blocks the sympathetic adrenergic and block the cholinergic (parasympathetic) so you will have large drop in BP because it caused disturbance. This drug is not used in Routine medicine it is only used in one condition in Emergency in case of Malignant increase of BP during cardiac surgery.

Sometimes during cardiac surgery, the BP increases and we cannot decrease it by alpha or beta blocker drugs that means if a drug that act mainly on Autonomic ganglia it decreases the BP on one injection and stop so therefore Trimethaphane is only used for Malignant crises of Hypertension in emergency in open cardiac surgery, otherwise there are no uses of this drug because of the many side effects from blocking adrenergic and cholinergic systems.

We have another type of neuron called the Motor neuron which releases *Acetylcholine*→ Act on the End plate (Striated Muscles) these receptors are called *Nicotinic Muscular* receptors (N.B Acetylcholine works on all muscles to produce contractions). When acetylcholine acts for long time with high dose these contractions and spasms will change into Paralysis because the receptors are down regulated or not effective then we have got Paralysis that means when the dose of acetylcholine increased do not always produce spasm it may cause paralysis at the end because of change in receptor binding to these drugs.

If I have a drug that block Muscarinic receptors → will lead to relaxation (No contractions) these drugs are called Muscle relaxants (e.g. Galamin and D-Tubocurarine).

So what is the use of Muscle relaxants? →they are used usually as premedication or pre-operation for operation to decrease the dose of Anesthesia to make the operation easy and to not have side effects of the Anesthetic drugs. There are new drugs but we study only about Galamin and D-Tubocurarine.

Site of action of acetylcholine are 5 sites:

1-The main site of action of acetylcholine is Ganglia (by stimulation or blocking).

2-On the motor neuron on End plate.

3-Postganglionic Parasympathetic neuron innervating the effector organ.

4- Postganglionic sympathetic or adrenergic system innervating sweat glands (which is activated by acetylcholine).

5- Central nervous system.

The action of Acetylcholine in CNS is increasing the Memory and Activity (e.g. Adrenaline and Nor-adrenaline).

- ✓ **Cholinergic Transmission**

The steps of Adrenergic Transmission are 5:

1. Biosynthesis of the Transmitter (e.g. Adrenaline, Nor-adrenaline, dopamine).
2. Storage.
3. Release.
4. Interaction with the receptor.
5. Inactivation or degradation.

In cholinergic system: (Exam quiz: Mention the steps of adrenergic or cholinergic system?) Concentrate on which system.

1. Biosynthesis (Acetyl CoA→ binds Choline → Acetylcholine + CoA → Acetylcholine is formed.
2. Storage → transported vesicles and stored.

3. Release: by activation → Action potential → Calcium in (Contraction) → fusion between vesicles and cell membrane and finally → release the content in synaptic gap.
4. Interact with receptors (effector organs).
5. Degradation: Acetylcholine → Choline and acetate → choline is again taken up into the neuron for formation of acetylcholine and acetate goes to the circulation. The degradation is done by the enzyme *Acetylcholinesterase.*

There are 2 types of Cholinesterases:

1. True Acetylcholinesterase:

   Only degrades endogenous Acetylcholine. If we have a drug that have same structure of Muscarinic or Nicotinic it is not degraded by this enzyme but it will be degraded by Butyrylcholinesterase (False)

2. False Acetylcholinesterase (Butyrylcholinesterase): degrade Acetylcholine and other drugs that have acetylcholine structure.

   What happen now in Degradation?

   Acetylcholine → binds the Acetylcholinesterase→ give Choline and acetate →Acetylcholine concentration will decrease → Termination of action of acetylcholine.

- ✓ **Drugs acting on it**

First we have to concentrate on the enzyme Acetylcholinesterase. If I have a drug that binds to this enzyme and block it is called *Cholinesterase inhibitor*. The result will be → No degradation → increase Acetylcholine concentration → it will work on Muscarinic and Nicotinic receptors → increase activity of the acetylcholine because of the cholinesterase inhibitor.

There are 2 types of Cholinesterase inhibitors:

1- Reversible cholinesterase inhibitors.

Increase in concentration of the agonist of Acetylcholine because of the weak binding it will be displaced so the effect of acetyl choline will return.

2- Irreversible cholinesterase inhibitors:

Strong binding to the enzyme or receptor and whatever the increase in the concentration but no maximal effect. So it will still work on the enzyme or receptor. Irreversible it will convert to reversible only after 24 hours. After 24 hours we can separate the irreversible.

Examples of Irreversible:

Parathion (insecticide) used in agriculture to kill insects. Qat poisoning because of Parathion by irreversible cholinesterase inhibition→ increase Acetylcholine concentration → Increase Activity of Muscarinic and nicotinic receptors will lead to:

(Question by the Dr. What are the signs and symptoms of Parathion Poisoning?)

1- On Bronchial smooth Muscles (Muscarinic) → Contraction →Dyspnoea (the first sign).
2- On Heart (Muscarinic 2) → decrease cardiac contractility →Decrease heart rate →Bradycardia.
3- On Blood Vessels (Muscarinic) → Vasodilation → Hypotension
4- On Glands (Muscarinic) →increase glands secretion → Salivation, if the gland is sweat there will be sweating. If the gland in the Eye, it will cause lacrimation.
5- On the Muscles → spasms.
6- On GI tract →Abdominal pain because of contractions could cause Diarrhoea.
7- Convulsion and Paralysis.

It is a very dangerous situation we should treat this How is the treatment?

You remember irreversible Acetylcholinesterase inhibitors (after 24 hours). Patient should be treated during 24 hours. The Drugs Are Atropine and pralidoxime. Atropine is a muscarinic blocker but acetylcholine will still work on nicotinic receptors, we need another drug that decrease the effect on nicotinic receptors but we don't have a drug that act on nicotinic receptors. We have pralidoxime→ an enzyme activator → binds with the enzyme and separate parathione from the enzyme (Displace parathione) but during 24 hours we can save the patient by giving the enzyme activator. Now the enzyme is active because we displaced the poison (parathione) → it will degrade acetylcholine and will decrease the effect on nicotinic receptors.

Treatment of poisoning with parathione depends on:

1- 24 hours for activation of the enzyme (Acetylcholinesterase) by Pralidoxime.
2- Decrease concentration of acetylcholine decrease the nicotinic effect. This is an indirect effect caused by pralidoxime but atropine can block directly.

Other irreversible acetylcholinesterase inhibitors are Nerve Gases:

1- Soman
2- Sarine

Some nerve gases used during demonstrations to prevent people from gathering they are used by security forces. The terrorists in Tokyo used Sarine in tunnels.

Sarin works on cholinergic system.

How is the treatment in Nerve gas inhalation?

Increase Acetylcholine concentration →dyspnea , Spasm, Sweating and so on. Atropine and Pralidoxime are the treatment. Atropine has Muscarinic effect (Blocker) and Pralidoxime decrease nicotinic stimulation by enzyme activation (Displacement).

The reversible drugs:

1- Neostigmine (Act mainly peripheral)
2- Physostigmine (Act mainly Central)

Neostigmine → a cholinesterase inhibitor → increase Acetylcholine in periphery → produce the same toxic effects (mentioned before).

Physostigmine→ its antidote is Atropine (N.B Atropine is the antidote of reversible and irreversible inhibitors).

Neostigmine is usually used when we have Atonia after Orthopaedic operation which takes long period of time, the patient will have no contractions in his GI tract so by giving Neostigmine we increase the contractions by increasing acetylcholine. Another way is by giving Muscarinic activators so we have now 2 ways in this case of Orthopaedic surgery.

Pravistigmine→ this drug is used for Alzheimer's disease, it act mainly central. It is used for Alzheimer's disease because it increases acetylcholine→ Increase Memory. So we improve the memory and attention in elderly patients. There are studies that proved that why we use this drug.

We talked about the drugs that are cholinergic inhibitors, now we go to the next group of drugs:

The firsts drugs mentioned before act on cholinergic system the second group we have Agonists and Antagonists. We have 2 types of cholinergic receptors Muscarinic and Nicotinic.

Muscarinic receptors Agonist on Muscarine lead to all the effects mentioned before (e.g. Arecoline and Betahnicol and so on). Arecoline and Bethanicol are muscarinic agonists (Arecoline a substance present in Betel nut).

There are no drugs act on nicotinic receptors except nicotine found in smoking cigarette.

Antagonist drugs we have 2 types:

1- On Nicotinic receptor (e.g. Ganglionic blockers because it blocks nicotinic ganglionic receptors and also nicotinic muscle relaxants). Muscle relaxant Galamin block nicotinic muscular receptor and Trimethaphan is a ganglionic blocker.
2- On Muscarinic receptors (e.g. Atropine)

Question: What are the main consequences of blocking muscarinic receptors?

Question: What is the effect of Atropine? The effects mentioned before, e.g. bronchodilation.

Now If I have a patient with Bronchial Asthma I can treat him by 2 ways:

1- Beta2 stimulant agonist (e.g. Salbutamol) →Bronchodilation.
2- Muscarinic Blocker (Muscarinic Antagonist) (e.g. Atropine) but it has no high effect. Hyoscine Bromide (Buscopan) has more effect than Atropine on Bronchial Muscle that's why when patient with Asthma has abdominal pain we give him Buscopan. Also Ibrathropum Bromide is used in Bronchial Asthma.

So What are the uses of Muscarinic Blockers (Antagonists)?

1- In Bronchial Asthma
2- Abdominal spasm
3- Glaucoma (Mydriasis)
4- In Glands (decrease secretion)

This is the action of the group of Muscarinic blockers but there are differences in the uses of each drug of this group. For example, Atropine we will use it mostly to decrease bronchial secretion that's why in operations they give Muscle relaxants, anesthesia and give atropine to decrease bronchial secretions. In Abdominal spasm we will give Buscopan.

Question: Give the indication or uses of Muscarinic blockers? you will mention the 4 drugs. But when say give the indication of atropine it is used preferably to decrease Bronchial secretion

Table 5–1 • AUTONOMIC NERVOUS SYSTEM EFFECTS*		
Organ	Sympathetic Adrenergic Receptor Action	Parasympathetic Cholinergic Receptor Action
Heart	β_1—increased heart rate and contractility	Decreased heart rate and contractility
Blood vessels†	α_1—constriction β_2—dilation	Dilation
Bronchi	β_2—bronchial smooth muscle relaxation	Bronchial smooth muscle contraction
GI tract	α_1—sphincter contraction β_2—relaxation	Overall contraction relaxation of sphincter
Kidney	β_1—renin release	No effect
Urinary bladder	α_1—sphincter contraction β_2—wall relaxation	Wall contraction sphincter relaxation
Adipose tissue Eye	β_1—increased lipolysis α_1—radial muscle contraction with pupil dilation	No effect Sphincter muscle contraction with pupil constriction ciliary muscle contraction

*See also Figure 1-1.
†No direct parasympathetic innervation.

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